UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, DC 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/435,510	05/05/95	VALLE F	GCL266

18M2/0331

GENENCOR INTERNATIONAL INC
925 PAGE MILL ROAD
PALO ALTO CA 94304

EXAMINER	
PROUTY,R	

ART UNIT	PAPER NUMBER
1814	10

DATE MAILED: 03/31/97

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

1-File Copy

PTO-90C (REV. 2/95)

☆U.S.GOVERNMENT PRINTING OFFICE 1995-319-826

Office Action Summary	Application No. 08/435,510	Applicant(s) Valle et al.
	Examiner Rebecca Prouty	Group Art Unit 1814

☒ Responsive to communication(s) filed on *Nov 9, 1996*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *23-39* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *23-39* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *6*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Claims 1-22 have been canceled. Claims and newly presented claims 23-39 are still at issue and are present for examination.

Applicants' arguments filed on 1-9-97, paper No. 8, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claims 32-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 32 (upon which Claims 33-37 depend) is confusing in the recitation of "catalyzing reactions in the pathway of said host cell" as it is unclear what pathways this refers to. Did applicants intend this to recite "catalyzing reactions in the pathway of biosynthetic production of said desired compound" instead?

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 23, 27, 28 and 38 are rejected under 35 U.S.C. § 102(b) as being anticipated by Saier et al.

Saier et al. teach methods of selecting a Pts^-/$glucose^+$ cell comprising deleting the PTS genes (*ptsH* and *ptsI*), culturing the mutant cell using glucose as the sole available carbon source and selecting cells with a fast growth rate on glucose.

Applicants argue that Saier et al. did not select for fast growing cells having a growth rate of at least about 0.4/hr. This is not persuasive because the cells isolated by Saier et al. are fast growing as claimed. Table 1 shows that the PTS^-/glu^+ mutants have a generation time of 2 hrs.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary

skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 3, 5-16, and 20-22 are rejected under 35 U.S.C. § 103 as being unpatentable over the combined disclosures of Frost, Holms, Ingraham et al. and Saier et al.

Frost teaches the amplification of carbon flow into the common aromatic pathway by increasing the amount of one of the substrates (E4P) for the first committed step of this pathway (i.e., the DAHP synthetase catalyzed condensation of E4P and PEP)

by introduction of the transketolase gene into the host cell. He further teaches the introduction of one or more of the genes of the common aromatic pathway in such cells to further increase the amount of the desired final product.

Holms teaches that PEP within *E. coli* is consumed by several different metabolic pathways (i.e., the PTS system, pyruvate synthesis by pyruvate kinase, and oxaloacetate synthesis by phosphoenolpyruvate carboxylase) and the amount of PEP channeled into each of these pathways. Holms teaches that the PTS system consumes 66% of the PEP produced while only 3% of the PEP pool is channeled into aromatic amino acid synthesis.

Ingraham et al. teach that it would be advantageous to increase the supply of PEP in a cell used for production of a desired product, in particular aromatic amino acid production, by modifying an enteric bacteria such as *E. coli* to use an alternative pathway from the PTS system for glucose uptake such that PEP production is not obligately coupled to glucose transport.

Saier et al. teach methods of selecting a $Pts^-/glucose^+$ cell which uses the galactose permease to transport glucose comprising deleting the PTS genes (*ptsH* and *ptsI*), culturing the mutant cell using glucose as the sole available carbon source and selecting cells with a fast growth rate on glucose.

The disclosure of Frost of amplification of carbon flow into the common aromatic pathway by increasing the amount of one of the substrates (E4P) for the first committed step of this pathway would suggest to the ordinary skilled artisan the amplification of the other necessary precursor (i.e., PEP) of this enzymatic step as one this would assure that neither substrate for this enzyme would be in limiting supply. One of ordinary skill in the art would recognize that the supply of any precursor used by a cellular pathway could be amplified by either increasing the amount of the precursor synthesized (such as done by Frost for E4P) or by preventing the depletion of the precursor by other cellular pathways thereby increasing the amount of the precursor available to be used by the desired pathway. The disclosure of Holms that 66% of the cellular PEP is used by the competing PTS pathway would suggest to the ordinary skilled artisan that PEP

availability to the common aromatic pathway could be substantially increased by preventing PEP use by the PTS pathway. Furthermore, Ingraham et al. explicitly suggest this as an approach to increasing the level of carbon flow into the common aromatic pathway. The disclosure Saier et al. shows that it is possible to produce cells which are deleted in the PTS system yet still retain high growth rates on glucose (a carbon source normally transported by the deleted PTS system) by utilizing the galactose permease as a means of glucose transport. Therefore, it would have been obvious to one of ordinary skill in the art to produce a Pts^-/$glucose^+$ mutant of the host cells of Frost which exhibit high levels of carbon flow into the common aromatic pathway as one of ordinary skill in the art would reasonably expect such a mutant cell to divert higher levels of the cellular pool of PEP into the aromatic amino acid biosynthetic pathways and produce further increases in the amount of carbon flow into this pathway. It would have been further obvious to one of ordinary skill in the art to select for such cells with high growth rates as such cells would be expected to be most useful for producing large amounts of aromatic amino acids.

Furthermore, it would have been further obvious to one of ordinary skill in the art to further increase the amount of PEP diverted into this pathway by preventing its use by the other metabolic pathways which Holms teach that it is consumed by. As such it would have been obvious to further mutate the pyruvate kinase and pyruvate carboxylase genes as well.

Applicant's arguments that the cited references fail to provide sufficient motivation to increase PEP availability have been considered but are considered moot in view of the disclosure of Ingraham explicitly teaching that it would be advantageous to increase the supply of PEP in a cell used for production of a desired product, in particular aromatic amino acid production, by modifying an enteric bacteria such as *E. coli* to use an alternative pathway from the PTS system for glucose uptake such that PEP production is not obligately coupled to glucose transport

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca Prouty, Ph.D. whose telephone number is (703) 308-4000. The examiner can normally be reached on Monday-Friday from 8:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Wax, can be reached on (703) 308-4216. The fax phone number for this Group is (703) 305-7401.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Rebecca Prouty
Patent Examiner
Art Unit 1814